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Additional File 1: Cell adhesion heterogeneity reinforces tumour cell dissemination: novel insights from a mathematical model - Model details

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Formal description of the LGCA model

LGCA model

The LGCA model is defined on a discrete 2-dimensional square lattice $\mathcal{L}$ with periodic boundary conditions [2, 3]. The lattice-gas model used in our work is an extension of cellular automata with binary states that has first been used in statistical physics and fluid mechanics (see [1] for an overwiew). Each lattice node $\boldsymbol{r} \in \mathcal{L}$ is connected to its four nearest neighbours, forming its *von Neumann* neighbourhood $\mathcal{N}_{\boldsymbol{r}}$, by unit vectors $\boldsymbol{c}_i, i = 0, ..., 3$, called velocity channels. The total number of channels per node is defined by κ, ands $\beta := \kappa - 4$ is an arbitrary number of channels with zero velocity, called rest channels, in which $\boldsymbol{c}_i = 0$, $4 \leq i < \kappa$. Each channel can be occupied by at most one cell at a time. In occupied channels, the occupation state $\eta_i(\boldsymbol{r}) = 1, i = 1, ..., \kappa$, whereas for empty channels $\eta_i(\boldsymbol{r}) = 0$. If $\eta_i(\boldsymbol{r}) = 1$, the occupying cell's adhesive state is described by the variable $a_i(\boldsymbol{r}) \in \mathbb{R}^+ := [0, \infty)$. Occupation states $\eta_i(\boldsymbol{r})$ and adhesive states $a_i(\boldsymbol{r})$ of all channels in a node $\boldsymbol{r}$ give the node configuration $(\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r})$, formally defined as $(\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r}) := ((\eta_0, ..., \eta_{\kappa-1}), (a_0, ..., a_{\kappa-1}))(\boldsymbol{r}) \in \mathcal{E}_a := \{0,1\}^\kappa \times {\mathbb{R}^+}^\kappa$. Fig. 1 (a) illustrates the state space of the LGCA model.

LGCA dynamics are characterised by a transition operator $\mathcal{D} : \mathcal{E}_a \to \mathcal{E}_a, (\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r}) \mapsto (\boldsymbol{\eta}', \boldsymbol{a}'')(\boldsymbol{r})$, that updates a given node configuration $(\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r}, k) := (\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r})$ to a subsequent node configuration $(\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r}, k+\tau) := (\boldsymbol{\eta}', \boldsymbol{a}'')(\boldsymbol{r})$ at time $k+\tau \in \mathcal{K}$ and is simultaneously applied to each node $\boldsymbol{r} \in \mathcal{L}$ at discrete time $k \in \mathcal{K} := \{j\,\tau \mid j \in \mathbb{N}\}$. The time-step length $\tau \in \mathbb{R}^+$, $\tau > 0$ is constant.

We define $\mathcal{D}$ as the composition of two operators:

- The **deterministic adhesivity change operator**

  $$\mathcal{A} : (\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r}) \to (\boldsymbol{\eta}, \boldsymbol{a}')(\boldsymbol{r}) \tag{1}$$

  calculates new adhesive states $a'_i(\boldsymbol{r})$ for every cell at node $\boldsymbol{r}, 0 \leq i < \kappa$. To determine the new values for the adhesive states, we use an intracellular adhesion receptor regulation model on the basis of an ordinary differential equation (ODE) described below [eq. (4)].

- The **probabilistic reorientation operator**

$$\mathcal{R} : (\boldsymbol{\eta}, \boldsymbol{a}')(\boldsymbol{r}) \to (\boldsymbol{\eta}', \boldsymbol{a}'')(\boldsymbol{r}) \tag{2}$$

  redistributes cells together with their adhesive states within a node $\boldsymbol{r}$ according to a probability function P described below [eq. (14)].

Accordingly, $\mathcal{D} := \mathcal{R} \circ \mathcal{A}$.
After reorientation, cells in velocity channel $\boldsymbol{c}_i$ of node $\boldsymbol{r}$ are deterministically moved to channel $\boldsymbol{c}_i$ of the neighbouring node $\boldsymbol{r} + \boldsymbol{c}_i \in \mathcal{L}$ according to the translocation operator $\mathcal{T}_i : (\boldsymbol{\eta}', \boldsymbol{a}'')(\boldsymbol{r}) \mapsto (\boldsymbol{\eta}', \boldsymbol{a}'')(\boldsymbol{r} + \boldsymbol{c}_i)$ (see Additional file 7 for details) that is defined by

$$\mathcal{T}_i : (\eta_i', a_i'')(\boldsymbol{r}) := (\eta_i', a_i'')(\boldsymbol{r} + \boldsymbol{c}_i), \qquad i = 0, ..., \kappa - 1, \boldsymbol{r} \in \mathcal{L}. \tag{3}$$

Deterministic intracellular adhesion receptor regulation model
We describe the adhesion receptor concentration of individual cells positioned at $(\boldsymbol{r}, \boldsymbol{c}_i)$ at time k by an adhesive state variable $a_i(\boldsymbol{r}, k)$. To determine $a_i(\boldsymbol{r}, k)$, we use the following ODE [adapted from [4]]:

$$\frac{dy_i^{\boldsymbol{r}}(t)}{dt} = h^+(R_0 - y_i^{\boldsymbol{r}}(t)) - h^- y_i^{\boldsymbol{r}}(t) \tag{4}$$

with $y_i^{\boldsymbol{r}}(t)$ the concentration of adhesion receptors on the cell surface at continuous time $t \in \mathbb{R}_0^+$, $h^+, h^- \in \mathbb{R}$ the respective adhesion receptor association and dissociation rates, $R_0 \in \mathbb{N}$ the maximum adhesion receptor concentration. The initial condition is $y_i^{\boldsymbol{r}}(0) = y_0$ (see Table 1 in main text for chosen parameter values).
The solution of eq. (4) can be obtained analytically and is given by

$$y_i^{\boldsymbol{r}}(t) = c\,\mathrm{e}^{-(h^+ + h^-)t} + \frac{h^+ R_0}{h^+ + h^-}, \tag{5}$$

where $c \in \mathbb{R}$ is a constant of integration. Setting $t = 0$ gives

$$c = y_0 - \frac{h^+ R_0}{h^+ + h^-}, \tag{6}$$

where y_0 is the initial adhesion receptor concentration. The steady state of the ODE model [eq. 4] is given by $\frac{h^+ R_0}{h^+ + h^-}$.
We distinguish between *fast* and *slow* intracellular adhesion receptor regulation. For the *fast regulation mode*, we use a quasi-steady state approximation and assume that the steady state is reached almost instantly. In this case, we $y_i^{\boldsymbol{r}}(t)$ to $\frac{h^+ R_0}{h^+ + h^-}$ for $t \geq 0$.
For the *slow regulation mode*, we calculate an adhesive state according to the analytical solution of the ODE model [eq. (5)] for every discrete cellular automaton

time k and every cell. The continuous adhesion receptor concentration $y_i^{\boldsymbol{r}}(t)$ of a cell at $(\boldsymbol{r}, \boldsymbol{c}_i)$ is temporally discretised to give the adhesive state variable $a_i(\boldsymbol{r}, k)$ by passing the discrete time-step of the LGCA model to eq. (5) as an argument [Fig. 2 (a) and Additional file 7 (b)]. For the temporal update, let $a_i(\boldsymbol{r}, k+\tau)$ be the adhesive state at time $k + \tau \in \mathcal{K}$.

Heterogeneity in the intracellular adhesion receptor regulation model

We introduce intrinsic adhesion heterogeneity by assigning independent stochastic values to two ODE parameters, the initial adhesive state y_0 and the maximum adhesive state R_0 (Fig. 2). Heterogeneity in these parameters is achieved by randomly drawing values from a normal distribution for each cell before starting the simulation. The respective expected values $\langle y_0 \rangle$ and $\langle R_0 \rangle$ are fixed (Tab. 1 in main text). As a control parameter for the degree of heterogeneity, we use the coefficient of variation and denote it by γ

$$\gamma = \frac{\sigma_{y_0}}{< y_0 >} = \frac{\sigma_{R_0}}{< R_0 >} \tag{7}$$

where σ_{y_0} and σ_{R_0} are the standard deviations of y_0 and R_0, respectively. γ-values are chosen to be equal for y_0 and R_0. The rates h^+ and h^- are held constant and identical for all cells. Note that rates h^+ and h^- have different units compared to rates of second order reactions as $y_i^{\boldsymbol{r}}(t)$ is not a molar concentration but the actual number of adhesion receptors on the cell surface [4]. For the *fast regulation mode*, where we approximate eq. (4) by the steady state value, the parameter R_0 that determines the steady state value $\frac{h^+ R_0}{h^+ + h^-}$ is drawn from a normal distribution with the same parameters as above.

For modelling extrinsic cell density-dependent adhesion receptor regulation, we modify eq. (5) by considering a linear cell density-dependent weight. To account for changes in cell density within the circular core population, we normalise the local cell density with the average global cell density, such that

$$y_i^{\boldsymbol{r}}(t, \rho(\mathcal{N}_{\boldsymbol{r}}, k)) = \left[1 - \alpha + \alpha \left(\frac{\rho(\mathcal{N}_{\boldsymbol{r}}, k)}{\bar{\rho}(N, k)}\right)\right] \; y_i^{\boldsymbol{r}}(t), \quad \alpha \in [0, 1], \tag{8}$$

where α is an environmental control parameter and $\bar{\rho}(N, k)$ is the global average cell population density, defined as

$$\bar{\rho}(N, k) := \frac{1}{N} \sum_{\boldsymbol{r}=1}^{N} \sum_{i=0}^{\kappa-1} \frac{1}{\kappa} \; \eta_i(\boldsymbol{r}, k) \tag{9}$$

with $N := N(\boldsymbol{r}, k)$ the number of nodes in $\mathcal{L}$ with at least one occupied channel at time $k \in \mathcal{K}$ and, as before, κ the number of channels per node. The term

$$\rho(\mathcal{N}_{\boldsymbol{r}}, k) := \frac{1}{5} \sum_{j=0}^{4} \sum_{i=0}^{\kappa-1} \frac{1}{\kappa} \; \eta_i(\boldsymbol{r} + \boldsymbol{c}_j, k) \qquad \in \mathbb{R} \tag{10}$$

describes the local cell density in a neighbourhood $\mathcal{N}_{\boldsymbol{r}}$ at time $k \in \mathcal{K}$. To model a decrease in adhesive states with increasing cell density, we changed eq. (8) such that the density-dependent weighting term linearly decreases with increasing local cell density, i.e.

$$y_i^{\boldsymbol{r}}(t, \rho(\mathcal{N}_{\boldsymbol{r}}, k)) = \left[1 - \alpha\left(\frac{\rho(\mathcal{N}_{\boldsymbol{r}}, k)}{\bar{\rho}(N, k)}\right) + \alpha\right] \; y_i^{\boldsymbol{r}}(t), \quad \alpha = 1. \tag{11}$$

Probabilistic migration step guided by intracellular adhesion receptor concentration
To account for adhesive interaction between cells, we model a probabilistic preference of migration towards areas with high local cell densities, i.e. nodes with high cell numbers $n_{\boldsymbol{\eta}(\boldsymbol{r})} := \sum_{i=0}^{\kappa-1} \eta_i(\boldsymbol{r})$. Thereby, the strength of adhesive interactions depends on the adhesive states $a_i(\boldsymbol{r}, k)$ of the interacting cells. We weight the cell numbers by the adhesive states $a_i(\boldsymbol{r}, k)$ of the interacting cells. This gives a momentum $\boldsymbol{J} := \boldsymbol{J}(\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r})$ of a node configuration $(\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r})$, defined by

$$\boldsymbol{J}(\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r}) := \sum_{i=0}^{\kappa-1} \boldsymbol{c}_i \, \eta_i(\boldsymbol{r}) \, a_i(\boldsymbol{r}). \tag{12}$$

The vector sum of all momenta in $\mathcal{N}_{\boldsymbol{r}} \setminus \{\boldsymbol{r}\}$ gives a local adhesivity gradient $\boldsymbol{G}(\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r})$ around node $\boldsymbol{r} \in \mathcal{L}$, excluding $\boldsymbol{r}$ (Fig. 1), defined by

$$\boldsymbol{G}(\boldsymbol{\eta}, \boldsymbol{a})(\boldsymbol{r}) := \sum_{j=0}^{3} \sum_{i=0}^{\kappa-1} \boldsymbol{c}_j \, \eta_i(\boldsymbol{r} + \boldsymbol{c}_j) \, a_i(\boldsymbol{r} + \boldsymbol{c}_j). \tag{13}$$

The reorientation probability $P : (\boldsymbol{\eta}, \boldsymbol{a}')(\boldsymbol{r}) \to (\boldsymbol{\eta}', \boldsymbol{a}'')(\boldsymbol{r})$ depends on the post-reorientation momentum $\boldsymbol{J} := \boldsymbol{J}(\boldsymbol{\eta}', \boldsymbol{a}'')(\boldsymbol{r})$ and the pre-reorientation local adhesivity gradient $\boldsymbol{G} := \boldsymbol{G}(\boldsymbol{\eta}, \boldsymbol{a}')(\boldsymbol{r})$. To model adhesive interaction as attraction between cells depending on their adhesive states, we define the reorientation probability P such that it increases with the degree of alignment between $\boldsymbol{J}$ and $\boldsymbol{G}$ [Fig. 1 (b)]. Formally, we achieve this by using the scalar product of $\boldsymbol{J}$ and $\boldsymbol{G}$. We then define the reorientation probability P such that, at each node $\boldsymbol{r} \in \mathcal{L}$,

$$P((\boldsymbol{\eta}, \boldsymbol{a'}(\boldsymbol{r})) \to (\boldsymbol{\eta}', \boldsymbol{a}'')(\boldsymbol{r}))) := \frac{1}{Z(\boldsymbol{\eta}, \boldsymbol{a'})} \; \exp(\langle \boldsymbol{J}, \boldsymbol{G} \rangle) \, \delta_{\boldsymbol{\eta}\,\boldsymbol{\eta}'} \, \Pi_{\boldsymbol{a'}\,\boldsymbol{a''}}. \tag{14}$$

With Kronecker's delta $\delta_{\boldsymbol{\eta}\,\boldsymbol{\eta}'}$ defined as

$$\delta_{\boldsymbol{\eta}\,\boldsymbol{\eta}'} := \delta(n_{\boldsymbol{\eta}}, n_{\boldsymbol{\eta}'}) = \begin{cases} 1 & : \quad n_{\boldsymbol{\eta}} = n_{\boldsymbol{\eta}'} \\ 0 & : \quad \text{else,} \end{cases} \tag{15}$$

we ensure that the number of cells at each node $\boldsymbol{r}$ before reorientation $n_{\boldsymbol{\eta}}$ is equal to the number of cells after reorientation $n_{\boldsymbol{\eta}'}$, i.e the number of cells in $\boldsymbol{r}$ stays

constant during reorientation.
The function $\Pi_{\boldsymbol{a}'\,\boldsymbol{a}''}$ ensures that the adhesive states of all rearranged cells within the channels of a given node $\boldsymbol{r}$ are maintained. It is defined as

$$\Pi_{\boldsymbol{a}'\,\boldsymbol{a}''} := \begin{cases} 1 & : \quad a'_{\pi(i)} = a_i,\ i = 0, ..., \kappa - 1 \text{ for a permutation } \pi \text{ of } (0, ..., \kappa - 1) \\ 0 & : \quad \text{else.} \end{cases} \tag{16}$$

The term $Z(\boldsymbol{\eta}, \boldsymbol{a'})$ is a normalisation term such that P is indeed a probability. It is given by

$$Z(\boldsymbol{\eta}, \boldsymbol{a}) := \sum_{\boldsymbol{\eta}' \in \mathcal{E}_a} \exp(\langle \boldsymbol{J}, \boldsymbol{G} \rangle)\, \delta_{\boldsymbol{\eta}\,\boldsymbol{\eta}'}\, \Pi_{\boldsymbol{a}'\,\boldsymbol{a}''}. \tag{17}$$

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